VERIFICATION OF A TRANSLATION

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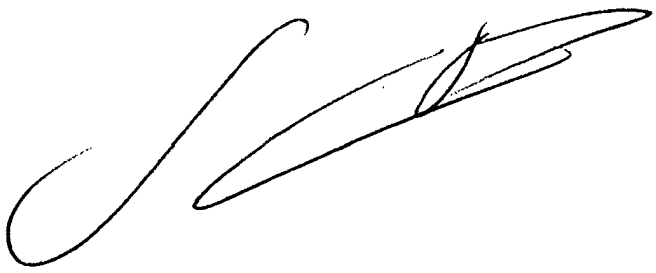
hereby declare that I am well acquainted with both the French and English languages and that the document attached is a true translation of the best of my knowledge and belief of the relevant parts of European patent application N° 1 077 061 filed on August 11, 2000, a copy thereof being also enclosed.

Signature of translator



Dated this October 23, 2009

US SERIAL N° 10/538 835

Translation by Gérard Portal, French and European Patent Attorney, of relevant parts of EP 1077 061 A2

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[016] The compositions of the invention can be in any form compatible with topical application to the surface of the mucosa of the bucal cavity. These compositions will preferably take the form of an emulsion of the oil-in-water or water-in-oil type, a cream, an ointment, a milk or a gel, particularly an oily gel based on colloidal silica.

[017] Nevertheless, the preferred form of compositions of the invention is that of an oily gel based on colloidal silica.

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[031] In the treatment and prevention of different affections of the bucal cavity given above, it will be used compositions which can be in the form of an emulsion of the oil-in-water or water-in-oil type, a cream, an ointment, a milk or a gel. Nevertheless, a particularly advantageous form will be that of an oily gel based on colloidal silica.

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Claims

9. Use according to one of the claims1 to 8, characterized in that said composition is in the form of an emulsion of the oil-in-water or water-in-oil type, a cream, an ointment, a milk or a gel, particularly an oily gel based on colloidal silica.
10. Use according to claim 9, characterized in that said composition is in the form of an oily gel based on colloidal silica.

EXHIBIT A

Volume 27 • Number 5 • October 2007

Journal of Clinical Psychopharmacology

Efficacy of a New Oral Lubricant Solution in the Management of Psychotropic Drug-Induced Xerostomia

A Randomized Controlled Trial

Stéphane J. Mouly, MD, PhD, Jean-Baptiste Orler, MD, Yves Tillet, PharmD, Anne-Claude Coudert, PharmD, Frantz Oberli, PhD, Phillip Preshaw, MD, and Jean-François Bergmann, MD

Efficacy of a New Oral Lubricant Solution in the Management of Psychotropic Drug-Induced Xerostomia

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Objective: Xerostomia is a subjective sensation of mouth dryness often occurring as an unwanted effect of psychotropic drugs.

Methods: The clinical efficacy and acceptability of a new oxygenated glycerol triester (OGT) oral spray (1 or 2 sprays up to 4 times daily) in the treatment of xerostomia was compared with those of a commercially available artificial saliva substitute (ASS [Saliveze]) in a 2-week, open-labeled, randomized, parallel-group study. Clinical assessment of xerostomia included evaluation of mouth dryness by means of a 10-cm-long visual analog scale, objective blinded assessment of the oral tissue condition by a dental hygienist by means of a 4-point ordinal scale, and subjective patient-based assessment of dry mouth symptoms by means of dichotomous responses to a questionnaire. [Day 14 − baseline] patient-based mouth dryness score was the primary end point.

Results: Seventy-four patients (41 women and 33 men, 44 ± 15 years) undergoing long-term psychotropic drug treatment were consecutively enrolled. At day 14, OGT resulted in better efficacy than ASS in mouth dryness score (mean difference, 1.2 ± 0.4; P = 0.006), speech difficulties (mean difference, 1.2 ± 0.4; P = 0.005), taste (mean difference, 1.1 ± 0.4; P = 0.02), and overall mouth condition (mean difference, 1.4 ± 0.9; P = 0.005). Taste of OGT was better than that of ASS (mean difference, 1.4 ± 0.6; P = 0.04), as was OGT acceptability (mean difference, 1.4 ± 0.9; P = 0.005).

Conclusion: Oxygenated glycerol triester lubricant oral spray was superior to a commercially available ASS in improving xerostomia and overall condition of the oral tissue.

(*J Clin Psychopharmacol* 2007;27:437–443)

Saliva plays a fundamental role in the maintenance of oral health and homeostasis. Lack of saliva predisposes individuals to oral symptoms and oral disease. Xerostomia is defined as the subjective sensation of dryness of the mouth that may or may not be associated with a marked decrease in saliva secretion and may frequently occur as an unwanted effect of psychotropic drugs.[1,2] Xerostomia is commonly associated with oral symptoms such as taste disturbances, bad breath, and mouth ulcers[3] and affects oral functions such as speech, chewing, and swallowing.[4,5] As a result, there is alteration in the microbial colonization of the oral cavity, reduction in prostheses retention, mucosal dehydration, and reduced lubrication in the oral mucosa.[6] These complications manifest as extensive dental caries, candidiasis,[7] mucosal atrophy and burning sensation, difficulty in denture retention,[8] compromised speech and swallowing, and reduced or altered taste sensation, thus restricting daily activities, along with a negative impact on quality of life.[9]

Management of xerostomia includes symptomatic relief, prevention or correction of the sequelae of saliva hypofunction, and treatment of any underlying disease. Adequate hydration of the oral tissues (frequent sips of water) is the standard treatment of xerostomia. Indeed, drug-induced xerostomia can sometimes be alleviated with chewing gum or taste stimulation using gustatory substances.[1–3] Other products available in the management of xerostomia, especially radiation-induced xerostomia or xerostomia occurring after removal of the salivary glands or in patients with Sjögren syndrome, include drugs known to stimulate the production of saliva such as pilocarpine or cevimeline.[2] However, in some patients with drug-induced xerostomia, it may no longer be possible to stimulate the normal saliva flow rate. In these patients, artificial saliva or saliva substitutes become the proper therapy.[2] The latter are usually formulated to be close to natural saliva in composition. They are typically based on aqueous electrolyte solutions and may contain animal mucins or carboxymethylcellulose. Mucin-containing saliva substitutes tend to result in slightly better improvement in xerostomia symptoms as compared with carboxymethylcellulose-containing saliva substitutes, but with poor acceptability by some patients.[10]

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Received December 10, 2006; accepted after revision May 18, 2007.

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ISSN: 0271-0749/07/2705-0437
DOI: 10.1097/jcp.0b013e31814db434

Oxygenated glycerol triester (OGT) oral spray (Aequasyal; Eisai SAS, Paris, France) is a new oral lubricant for the treatment of dry mouth. Oxygenated glycerol triester is supplied as an oral spray and contains no pharmacological ingredients but a lubricant compound, OGT (94.4%), silicon dioxide (1.5%), and alimentary-grade flavoring agents (4.1%). Because of the presence of OGTs and silicon dioxide, OGT spray has the property of adherence to the oral mucosa, forming a lipid film that protects against mechanical trauma and may help to reduce oral tissue moisture loss and inflammation. To a lesser extent, OGT oral spray may slightly stimulate saliva production because of the presence of small amounts of flavoring agents.[1,2,11] In the current study, we hypothesized that OGT oral spray, as an oral lubricant, may be effective in the subjective relief of dry mouth symptoms and objective signs of dry mouth in patients with xerostomia induced by long-term treatment with psychotropic drugs.

PATIENTS AND METHODS

Materials

The study was sponsored by Laboratoires Carilène (Montesson, France). Oxygenated glycerol triester oral spray was provided by the study sponsor (Laboratoires Carilène, Montesson, France). The positive control artificial saliva substitute (ASS [Saliveze]), also provided by the sponsor, is an aqueous electrolyte-containing solution (calcium chloride 0.15 mg/mL, magnesium chloride 0.05 mg/mL, sodium chloride 0.05 mg/mL, potassium chloride 1.2 mg/mL, sodium phosphate 0.28 mg/mL, and sorbitol 30 mg/mL) purchased from Wyvern Medical Limited (Herefordshire, UK). Each bottle of OGT and ASS contained 20 and 50 mL of solution, respectively.

Subjects, Aim, and Study Design

Our objective was to evaluate the clinical efficacy and acceptability of OGT oral spray in the relief of symptoms of xerostomia as compared with ASS. The latter was chosen as the reference product because it is a standard CE-marked, commercially available treatment of dry mouth and supplied as an oral spray similar to OGT.

A 2-week, randomized, parallel-group (to avoid any period, treatment, or carryover effect), open-labeled design was used. The open-labeled study design was chosen in the current trial because of the different texture of the 2 products (ASS is an aqueous solution, whereas OGT is a rather viscous oral lubricant). Patients, 18 years and older, treated with various psychotropic drugs and complaining of dry mouth, with confirmed low saliva output using a sialometer (test of saliva weight absorbed $\leq$0.5 g/5 min) at baseline and after stimulation by chewing gum (showing a mean saliva flow rate of $\leq$0.16 and $\leq$0.5 mL/min, respectively),[9,11,12] were enrolled after written informed content was obtained and then randomly assigned to either OGT or ASS spray treatment for 2 weeks. They were not allowed to use any other products for the treatment of dry mouth but could take sips of water. They were also allowed to use other mouth care products if needed (eg, topical analgesics, topical antiseptics, antifungal treatments). The randomization was based on a permuted blocks-of-4 design.

Demographic data and history of dry mouth were recorded, including details of the psychotropic treatment and history of psychiatric diseases. Patients completed a questionnaire to record symptoms of xerostomia at baseline (D0). Objective assessment of the oral tissue condition was recorded by a dental hygienist in a blinded fashion using a 4-point ordinal scale and included assessment of the lips, tongue, hard and soft palate, gingiva, mucobuccal fold areas, buccal mucosa, and floor of the mouth.[9,11] Each patient was given 2 bottles of either OGT or ASS, to ensure they had adequate quantities for the entire study. They were instructed to use 1 or 2 sprays of the assigned product up to 4 times daily, as necessary. The bottles of spray were weighed before dispensing to the patients and at the end of the treatment period to assess the quantity of product used and treatment adherence. This study was conducted in accordance with the Declaration of Helsinki and approved by the research ethics committee of the Cimiez-Victor University Hospital, Nice, France. It was registered with the ClinicalTrials.gov registry (no. NCT00332618).

Clinical Measurements and Questionnaires

The primary outcome variable was patient-based dry mouth score as evaluated by means of self-rated 10-cm-long visual analog scale (VAS) scores recorded at day (D) 0 and D14.[9,11] Anchor points of the VAS score were 0, representing normal (ie, no dry mouth symptoms), and 10, representing "the worst imaginable" dry mouth symptoms. The latter was chosen as the primary end point because it was a specific, sensitive, and reproducible criterion, consistent with the main objective of the current clinical trial.[11] Secondary outcome variables included subjective perception of changes in other dry mouth symptoms (ie, chewing, swallowing, and speech difficulties as well as taste and burning sensations) using self-rated 10-cm-long VAS. In addition, oral tissue condition was recorded by the dental hygienist in a blinded fashion at D14 (redness and dryness of the tissues, degree of inflammation) using a 4-point ordinal scale, as previously described.[9,11] The scale was calibrated as follows: 0 = none, 1 = mild, 2 = moderate, and 3 = severe defect. The dental hygienist who evaluated each patient was blind to the treatment. Results were expressed as mean score ± standard deviation (SD) obtained in the respective treatment groups.

Subjective assessment of xerostomia was performed at baseline and at D14 using dichotomous responses to a previously validated questionnaire[1] and included several criteria such as diurnal and nocturnal mouth dryness, sleep disturbances due to mouth dryness, bad taste sensation, and use of saliva substitute, as well as questions indicating social life restrictions, that is, "Do you avoid speaking to people because of your dry mouth?" and "Do you stay home because of your dry mouth?"

Evaluation of Treatment Tolerance and Acceptability

Treatment tolerance, acceptability, and taste were evaluated by means of a self-rated 10-cm-long VAS. Adverse events were recorded by the investigator.

Statistical Analysis

Statistical analysis was implemented in SPSS v.12.0 for Windows (SPSS Inc, Chicago, Ill). Data were presented as mean ± SD of the [D14 − baseline] differences for VAS scores and 4-point ordinal scales, respectively. Two-tailed comparisons of [D14 − baseline] differences in primary and secondary end points were made between treatments with respect to demographic and efficacy parameters, according to the intent-to-treat principle. Because of the lack of any published data regarding the efficacy of OGT oral spray, the power calculation was estimated based on data derived from previously published studies of treatments for xerostomia.[11,12] Hence, assuming a within-group SD of 1 cm in the VAS score, a power of 85%, and a type I error rate of 0.05, a sample size of 33 patients in each treatment arm was required to demonstrate an effect size of 0.75. Allowing for a dropout rate of approximately 10%, the target was set for 74 patients to be recruited in the current study. To compare the effectiveness of one product against the other with respect to continuous variables relating to effectiveness of spray at D14, the [D14 − baseline] differences in primary and secondary end points were compared using a 2-tailed, unpaired Student t test; χ^2 or Fisher exact tests were used to determine the significance of differences (if any) between dichotomous response variables between the 2 treatment groups, where appropriate. A 2-tailed, independent Mann-Whitney U test was used to determine the significance of differences (if any) in the objective assessments of oral status between the 2 groups. Given that some of the objective assessments of oral status were related to each other and to increase the number of patients per item, a further analysis was performed, combining related data, that is, assessment of overall dryness of mouth that included assessment of dryness, inflammation, redness, stickiness, dullness of oral mucosa, and severity of mucositis. This combination was assessed using Cronbach α internal reliability scale. A P value of 0.05 was set as the level of statistical significance for each comparison performed.

RESULTS

Demographic Characteristics at Baseline

Among the 96 patients approached to participate in the study, 74 (41 women and 33 men) signed the written informed consent before being enrolled. All but two completed the study. Mean age (44 ± 15 years; range, 18–88 years), weight (66 ± 14 kg; range, 32–110 kg), and height (167 ± 9 cm; range, 140–186 cm) did not differ between treatment groups (respectively, $P > 0.1$, 2-tailed, unpaired Student t test). Likewise, sex ratio did not differ between groups ($P = 0.64$, χ^2 test). Bipolar disorder was noted in 50% of patients. Remaining psychiatric disorders for which patients received psychotropic drugs included depression in 26% of cases, schizophrenia in 7% of cases, social anxiety disorders and obsessive-compulsive disorders in 7% of cases, and major anxiety in 3% of cases. Fifty-three drugs, totaling 221 prescriptions (ie, 2.99 drugs per patient), were taken by the 74 patients at the time of the study. These included antidepressants in 59 cases (citalopram, clomipramine, paroxetine, sertraline), benzodiazepines in 55 cases (bromazepam, dipotassic clorazepate, prazepam), antipsychotics including neuroleptics in 47 cases (cyamemazine, olanzapine, risperidone), hypnotics in 36 cases (zolpidem, zopiclone), meprobamate in 11 cases, anticonvulsants and lithium carbonate in 8 cases (carbamazepine, lithium carbonate, valpromide), and levodopa in 5 cases. Medical history was otherwise unremarkable except for alcohol abuse in as much as 10% of patients. Hyposalivation was objectively confirmed upon enrollment by measurement of saliva output (in milliliters per minute) using a sialometer, showing a mean saliva flow rate less than the normal border of 0.16 mL/min (see Patients and Methods), and did not differ between treatment groups (0.04 ± 0.2 vs. 0.03 ± 0.2 mL/min). Eleven patients (15%) were using a saliva substitute at the time of the study. Seven of these used anetholtrithione (Sulfarlem S25), whereas the 4 remaining patients preferred chewing gum.

TABLE 1. Mean [D14 − Baseline] Differences in Primary and Secondary End Points, as Determined Using Self-rated 10-cm VAS for Assessment of Dry Mouth Symptoms, According to Treatments

	[D14 − Baseline] Difference, cm		
Items*	OGT (n = 37)	ASS (n = 37)	Mean Between-Treatment Difference, cm
Mouth dryness	−5.8 ± 2.8	−4.6 ± 2.3	1.2 ± 0.4†
Chewing difficulties	−4.3 ± 3.5	−3.3 ± 2.7	0.5 ± 0.8
Swallowing difficulties	−4.8 ± 2.9	−4.0 ± 2.8	0.5 ± 0.1
Speech difficulties	−5.7 ± 2.7	−4.5 ± 2.3	1.2 ± 0.4†
Taste	−4.5 ± 3.4	−3.1 ± 2.8	1.1 ± 0.4†
Burning sensation	−2.7 ± 2.6	−2.9 ± 3.2	0.1 ± 0.3

*[D14 − baseline] differences and between-treatment difference scores are presented as mean ± SD.

†$P = 0.006$ for mouth dryness, $P = 0.005$ for speech difficulties, and $P = 0.02$ for taste (2-tailed unpaired Student t test).

At baseline, most patients complained of severe dry mouth (>8 cm), as measured by a 10-cm-long VAS (Table 1). Fifty-five percent (41/74) of them were wearing a denture (21 in the OGT group and 20 in the control group). Denture retention was affected by mouth dryness in only 28.6% (6/21) and 20% (4/20) of patients in the OGT and ASS groups, respectively (P = 0.72, Fisher exact test). Ninety-nine percent of patients presented with moderate to severe dry mouth according to the dental hygienist's objective assessment at baseline. Likewise, 96% of patients presented with oral mucosal inflammation, more than half of them being moderate to severe. Thirty-three percent (24/74) of patients presented with severe mucositis, and 51% of patients presented with at least 1 abrasion of the oral mucosa. Overall, only 4 patients in each treatment group had moderate (n = 3) to severe (n = 1) oral abrasions. Seventy-eight percent (55/74) of patients presented with damaged lips and/or thickened tongue. Almost 50% of patients treated with OGT oral spray had mild lip damage as compared with only 19% of patients treated with ASS. Conversely, 48.6% of patients in the control group had moderate or severe lip damage as compared with 32.4% in the OGT group (P = 0.02, Fisher exact test). Sixty-one percent (45/74) of patients presented with viscous saliva. Moderate or severe viscous saliva, however, was noted in less than 25% of patients and did not differ between treatment groups (Table 2). In addition, 73% (54/74) of patients had moderate to severe speech difficulties related to dry mouth.

Efficacy of OGT Oral Spray Based on the Primary and Secondary End Points at D14

All but 2 patients (72/74) completed the study. Data were lacking for 1 patient (ASS group) at D14. Another patient (OGT oral spray group) was excluded because of protocol violation. These patients, however, were included in the final analysis according to the intent-to-treat principle. Data regarding these patients were estimated based on the mean (continuous variables) or median (nominal variables) of the respective treatment group. Of the 6 symptoms self-rated on a 10-cm-long VAS at D14, OGT resulted in significantly better efficacy than ASS in 3 items, that is, mouth dryness (P = 0.006), defined as primary end point, speech difficulties (P = 0.005), and taste improvement (P = 0.02), after adjustment for differences at baseline (Table 1). The sensation of improvement started on the second day of treatment in 55% and 83% of patients in the ASS and OGT groups, respectively, and lasted up to 4 hours after each oral spray for the majority of patients.

D14 Patient-Based Assessment of Symptoms

At baseline, 99% and 66% of patients complained of diurnal and nocturnal mouth dryness, respectively. Almost 45% of them woke up because of mouth dryness. Likewise, 65% of patients had a bad taste in their mouth. No difference was noted between treatment arms at baseline (P > 0.2, Fisher exact test). At D14, OGT spray improved chewing, swallowing, and speech in 73%, 65%, and 60% of cases, respectively, as compared with 53%, 47%, and 58% of patients treated with ASS (P = 0.08, P = 0.18, and P = 0.55, respectively, Fisher exact test). Taste, burning sensation, and social life items, that is, dichotomous responses to questions such as "Do you stay at home more because of your dry mouth?" and "Do you avoid speaking to people because of your dry mouth?" which were mentioned by up to 56% of patients at baseline, were improved overall by either oral

TABLE 2. Mean [D14 − Baseline] Differences in the Oral Condition Parameters Recorded by the Blinded Dental Hygienist Using 4-Point Ordinal Scale

Items*	[D14 − Baseline] Difference		Between-Treatment Difference†
	OGT (n = 37)	ASS (n = 37)	
Overall dryness of mouth	−1.7 ± 0.8	−1.6 ± 0.8	0.1 ± 0.2
Dryness of oral mucosa	−1.2 ± 0.4	−1.2 ± 0.7	0.1 ± 0.1
Inflammation of oral mucosa	−1.1 ± 0.8	−1.2 ± 0.9	0.1 ± 0.2
Redness of oral mucosa	−1.0 ± 0.5	−1.2 ± 1.0	0.2 ± 0.3
Stickiness of oral mucosa	−1.1 ± 0.6	−1.2 ± 0.9	0.1 ± 0.3
Dullness of oral mucosa	−1.3 ± 0.8	−1.0 ± 0.8	0.3 ± 0.1
Severity of mucositis	−0.3 ± 0.6	−0.5 ± 0.8	0.2 ± 0.2
Oral mucosal abrasion and ulcerations	−0.6 ± 0.8	−0.9 ± 0.9	0.2 ± 0.1
Damaged lips	−1.1 ± 0.8	−1.1 ± 0.9	0.05 ± 0.1
Thickened tongue	−0.7 ± 0.7	−0.8 ± 0.9	0.1 ± 0.2
Deficiency of saliva	−1.3 ± 0.5	−1.3 ± 0.9	0.1 ± 0.1
Viscosity of saliva	−0.6 ± 0.7	−0.7 ± 0.8	0.1 ± 0.3
Foamy quality of saliva	−0.5 ± 0.7	−0.6 ± 0.9	0.1 ± 0.3
Halitosis	−0.8 ± 1.1	−0.9 ± 0.8	0.1 ± 0.2
Speech difficulties	−1.0 ± 1.0	−1.1 ± 1.3	0.05 ± 0.1
Saliva and crusting at corners of mouth	−0.4 ± 0.7	−0.5 ± 0.9	0.05 ± 0.1

*[D14 − baseline] differences and between-treatment difference scores are presented as mean ± SD.
†P > 0.14 for all comparisons between treatments (2-tailed, unpaired Mann-Whitney U test).

spray, according to patient-based assessment of symptoms. Fifty-six percent of patients treated with ASS and 76% treated with OGT declared that their oral spray was as effective during the day as during the night ($P = 0.2$, Fisher exact test).

Objective Assessment of Oral Condition at D14 by Means of a 4-Point Ordinal Scale

Table 2 presents assessment of oral condition as recorded by the dental hygienist at D14 with respect to treatment. The oral condition was significantly improved by both oral sprays, as shown by a mean 65% decrease in the score of each item as compared with baseline. No significant differences between the 2 treatment options were found. Nevertheless, some interesting clinically relevant differences between the two were observed during the 2-week treatment period, for example, overall dryness of mouth and mucosa, inflammation, redness, stickiness, dullness of oral mucosa, deficiency of saliva, and improvement in speech difficulties (Table 2). Given that some of the objective assessments of oral status were related to each other and to increase the number of patients per item, further analysis was performed combining related data, that is, assessment of overall dryness of mouth, dryness, inflammation, redness, stickiness, dullness of oral mucosa, and severity of mucositis, to produce a scale that had high internal reliability, as ascribed by a Cronbach α coefficient of 0.85. Even when combining these variables into a single model, the difference between treatment groups remained nonsignificant at D14 after adjusting for baseline value ($P = 0.62$). The remaining items assessing saliva as well as the presence of halitosis, mucosal abrasion, damaged lips, and speech difficulties (Table 2) were not strongly correlated and could not be added to the model to build a scale that was internally consistent (Cronbach $\alpha = 0.07$).

Treatment Tolerance and Acceptability

No serious adverse event was reported during the study. Minor adverse events were noted in 4 patients (4.6% of cases) and included nausea (n = 1, ASS group) and unpleasant taste (n = 1, ASS group; n = 2, OGT group). Both oral sprays were qualified as easy to use by 90% of patients. More than 85% of patients were willing to continue their spray after the end of the study, although the taste of OGT was preferred to that of ASS (7.2 ± 2.2 vs. 5.8 ± 2.9; mean difference, 1.4 ± 0.6; $P = 0.04$, Mann-Whitney U test). Global treatment acceptability at D14 was significantly better for OGT, as assessed by global mouth sensation after each spray administration using the self-rated 10-cm-long VAS (6.3 ± 2.6 vs. 7.7 ± 1.6 in the ASS and OGT groups, respectively; mean difference, 1.4 ± 0.9; $P = 0.005$, Mann-Whitney U test).

DISCUSSION

In clinical practice, xerostomia is often underestimated by clinicians and patients themselves, presumably because the efficacy of currently available therapeutic options is highly unpredictable.[13] Based on extensive evaluation of clinically relevant symptoms of xerostomia,[1,11,12,14,15] the current prospective randomized controlled study conducted in patients under real conditions of treatment by psychotropic drugs for various psychiatric and neuropsychiatric disorders, with drug-induced xerostomia and confirmed severe hyposalivation,[16–18] demonstrated that a 14-day treatment with OGT oral spray was significantly more effective than ASS, specifically in improving mouth dryness, speech difficulties, and taste, as assessed by means of VAS. The 2 oral sprays were equally effective in significantly improving mouth condition, especially oral mucosa status and dryness of mouth and oral mucosa (Table 2).

It is difficult to make the initial clinical decision as to whether a given patient has salivary gland hypofunction with symptoms of xerostomia and hence requires additional salivary gland evaluation and whether he or she may be eligible for treatment. In this regard, and apart from the use of a previously validated questionnaire[1] rather than the recently published xerostomia inventory,[19] we used validated tools (eg, 10-cm-long VAS and 4-point ordinal scale) and a validated cutoff of salivary flow rate to relevantly identify and enroll patients with dry mouth for the purpose of the current clinical trial.[9,11,12,20] Despite the clinical relevance of the enrolled population and the observed treatment efficacy, the current study has several limitations, partly related to the difficulty in evaluating treatments in such a subjective condition as xerostomia. The short-term parallel design of the trial requires further evidence of continued efficacy of OGT oral spray in the relief of dry mouth symptoms. A longer, crossover clinical study would have been helpful to demonstrate the efficacy of OGT oral spray over time in psychiatric patients with drug-induced xerostomia caused by long-term treatments.[21] The open-labeled study design chosen in the current trial because of the different texture and taste of the 2 products (ASS is an aqueous solution, whereas OGT is a rather viscous oral lubricant containing alimentary-grade flavoring agents) may limit the reliability of the results and require further confirmation in a future, double-blind, randomized controlled trial conducted in a larger cohort of patients. In addition, although OGT may have slightly enhanced saliva production because of the presence of small amounts of a flavor,[21] neither oral spray stimulated saliva production, and saliva output was therefore only measured upon patient enrollment to confirm hyposalivation but not upon treatment completion at D14. Finally, the purpose of the current study was to compare OGT oral spray with a currently marketed saliva substitute (and not with pilocarpine hydrochloride, the reference treatment of dry mouth[2]) in the relief of symptoms of xerostomia, but not to correlate treatment efficacy to the decrease in saliva output in our patients, the latter not being established to the best of our knowledge.[2,12,14,20]

There are more than 500 medications that report dry mouth as a side effect, but only a small number, however, have been shown to result in actual reduced salivation. These include tricyclic antidepressants, antihistamines, antihypertensives, and diuretics.[15–18,22–24] Salivation is dependent on parasympathetic, especially muscarinic-dependent, stimulation that induces dilation of the oral

mucosal blood vessels and myoepithelial cell contraction.[25,26] In addition, the central nervous system controls saliva secretion in response to several common stimuli, for example, taste or smell. β-Adrenergic–dependent sympathetic stimulation, but also serotonin, may enhance glycoprotein secretion in the saliva, which in turn enhances oral cavity lubrication.[25,26] Numerous drugs, including psychotropic drugs,[3,15–18,22] directly act on the sympathetic and parasympathetic pathways, thus decreasing salivary output and modifying the quality of saliva without directly structurally affecting salivary glands, with effects in the oral cavity.[24–26] Moreover, an additive effect has been previously observed when several psychotropic agents are associated in the same patient, which was the case in the current study, with a mean of almost 3 concomitant psychotropic drugs per patient.[3] Drug-induced, especially psychotropic drug-induced, xerostomia is often neglected by physicians as it has long-term, especially severe dental, rather than immediate consequences on the oral condition.[3,13] In some instances, eating as well as social life may be severely impaired in some patients, especially in the elderly who frequently take numerous concomitant medications.[3,13,15,16] In psychiatric patients, the prevalence of severe xerostomia with restriction of daily activity may be as high as 29%,[16] consistent with our patients.

Dry mouth evaluation should be carried out in a systematic fashion, as performed in the current study. In clinical practice, the goals are to document salivary function and to determine the cause for any dysfunction found. The results of such evaluation may help provide guidance for the development of a rational, comprehensive management plan.[1] The adoption of 1 treatment option from among the different options available depends on the cause underlying xerostomia and on the functionality of the saliva glands.[2] In any event, the goals are to relieve symptoms, prevent or correct the sequelae of salivary dysfunction, and treat any underlying disease. Given the mechanisms involved in psychotropic drug-induced xerostomia, adequate hydration of the oral mucosa to moisten and cleanse the mucosal surface and to hydrate the oral tissue is essential. As mentioned above, many saliva substitutes are currently available on the market.[1,2,7,10,12,14] The majority of dry mouth patients do not use saliva substitutes regularly. In some authors' experience,[24] most patients find that frequent sipping of fluids is superior and more esthetically acceptable than applications of saliva substitutes. The current study does not confirm these observations. Indeed, 90% of patients, most of them with severe depression and/or psychosis, endorsed both oral sprays as easy to use, and acceptability of the 2 products was high, as assessed by means of a self-rated VAS. More than 85% of patients were willing to continue using oral sprays after the end of the study.

To date, only a few randomized controlled trials have addressed the problem of relief of psychotropic-drug induced xerostomia. In a previous randomized controlled trial enrolling 94 patients with symptomatic hyposalivation caused by senile hypofunction, medications, or oral cancer therapy and comparing the bile secretion–stimulating drug, anethole trithione, to a commercially available saliva substitute, the cholagogue significantly increased saliva flow rate in all 49 patients, especially those with drug-induced xerostomia, as compared with those treated with the saliva substitute, and there was significant relief of oral discomfort and inflammation.[12] In another randomized, open-labeled, placebo-controlled trial conducted in healthy volunteers treated with the opioid analgesic, tramadol, to induce hyposalivation, oral pilocarpine significantly restored saliva flow rate as compared with placebo.[14] However, except for a self-based assessment of the sensation of a decrease in saliva production, no evaluation of dry mouth symptoms or oral cavity was performed in this study.[14] Finally, in a more recent randomized controlled crossover study comparing 3 mildly flavored sodium lauryl sulfate–containing and detergent-free toothpastes with or without betaine in 27 patients with xerostomia and 18 healthy controls using VAS score for patient evaluation, the authors observed that the betaine-containing toothpaste relieved dry mouth symptoms in 44% of patients, which is close to the observed 55% of patients treated with ASS who mentioned symptom relief, but much lower than the observed 83% of patients with symptom relief after the second day of treatment with OGT.[21]

In conclusion, using a systematic approach and aggressive management, most patients with dry mouth can achieve oral comfort and adequate oral function.[20–24] In this regard, the current study showed that OGT oral spray was more effective than a currently marketed ASS containing electrolytes in improving some but not all evaluated symptoms of psychotropic drug-induced xerostomia, such as oral mouth dryness, speech difficulties, taste, and overall mouth condition. Given the limited efficacy of some treatments such as gustatory substances[21] and chewing gum, we believe that OGT oral spray may be proposed in the management of psychotropic-drug induced xerostomia, especially when sialogogues such as pilocarpine may be hard to use because of increased risk of cardiovascular side effects.[2,14–16] Further studies will be needed to determine whether the efficacy of OGT oral spray may be prolonged over time in the clinical setting. Increasing numbers of isolated or concomitant prescriptions of antidepressants and benzodiazepines in primary and specialty care settings should warn physicians on the risk of invalidating xerostomia with or without hyposalivation and its consequences on oral health, daily activity, and maybe adherence to long-term psychotropic treatments.

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Reprinted from
Drugs & Aging 2007; 24 (11): 957-965
ISSN: 1170-229X

Drugs & Aging

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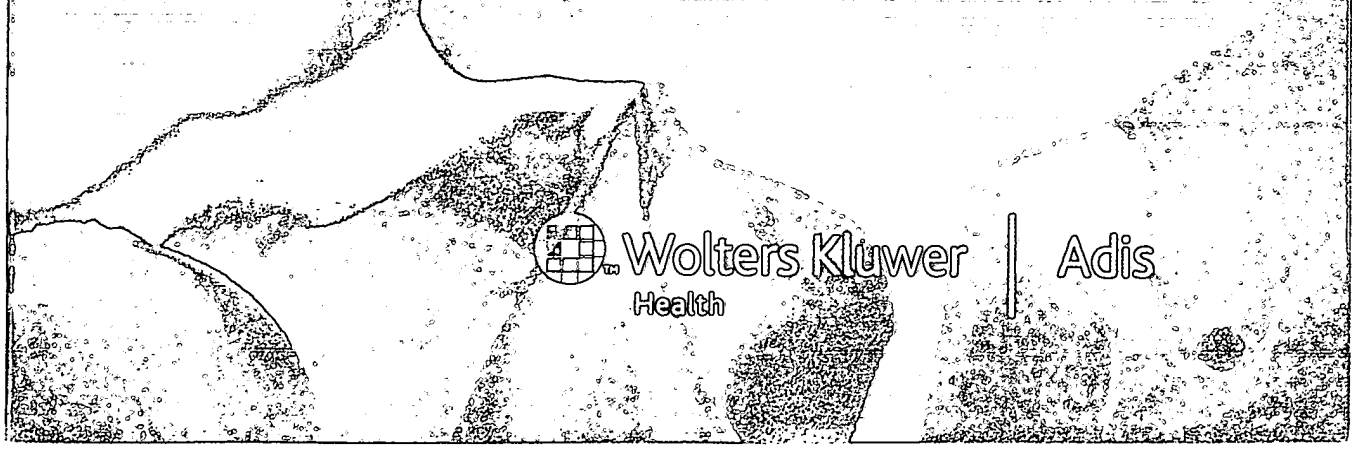

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Drugs & Aging (ISSN 1170-229X) is published annually as 1 volume with 12 issues by Wolters Kluwer Health | Adis. The annual 2007 institutional subscription price for print and online is $US2715 and for online only is $US2680. The personal subscription price for print and online is $US295 and for online only is $US290. All online subscriptions include access to online archived articles. Further subscription information is given at the back of each issue.

ORIGINAL RESEARCH ARTICLE

Drugs Aging 2007; 24 (11): 957-965
1170-229X/07/0011-0957/$44.95/0

Management of Xerostomia in Older Patients

A Randomised Controlled Trial Evaluating the Efficacy of a New Oral Lubricant Solution

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Abstract

Background: Xerostomia is a subjective sensation of mouth dryness that may frequently occur in older patients.

Objective: To compare the clinical efficacy and acceptability of a new oxygenated glycerol triester (OGT) oral spray taken five times daily with that of a commercially available saliva substitute (Saliveze®) in the treatment of xerostomia.

Methods: Forty-one institutionalised patients (28 women, 13 men; mean age 84 ± 7 years) were randomly assigned to receive either OGT or Saliveze® in a 2-week, randomised, parallel-group study. Clinical assessment of xerostomia included evaluation of mouth dryness using a self-rated, 10cm long visual analogue scale (VAS), objective assessment of oral tissue condition using a four-point ordinal scale and subjective assessment of symptoms of xerostomia using dichotomous responses to a questionnaire. The primary endpoint was the day (D) 14 patient-based mouth dryness score measured on a self-rated VAS.

Results: At D14, OGT resulted in significantly greater efficacy with respect to mouth dryness (mean between-treatment difference 2.1 ± 0.1, 95% CI 1.9, 2.3; p = 0.001), swallowing difficulty (1.8 ± 0.3, 95% CI 1.5, 2.1; p = 0.001), speech difficulty (1.1 ± 0.2, 95% CI 1.0, 2.4; p = 0.04) and overall sensation of symptom relief (2.7 ± 1.2, 95% CI 1.9, 3.8; p = 0.001). Objective assessment of oral tissues also showed significantly better improvement with OGT spray with respect to dryness (p = 0.01), stickiness (p = 0.005) and dullness (p = 0.001) of oral mucosa; severity of mucositis (p = 0.01); and thickening of the tongue (p = 0.03). A significant difference in taste acceptability was also noted in favour of OGT (1.4 ± 0.6, 95% CI 1.2, 1.9; p = 0.04).

Conclusion: OGT lubricant oral spray was superior to Saliveze® in improving xerostomia and oral tissue condition in older institutionalised patients.

Introduction

Saliva plays a fundamental role in the maintenance of oral health.[1] Salivation is dependent on parasympathetic, especially muscarinic-dependent, stimulation that induces dilation of the oral mucosal blood vessels and contraction of the myoepithelial cells.[2,3] In addition, β-adrenergic-dependent sympathetic as well as serotonin stimulation by the CNS control saliva secretion in response to several common stimuli, for example, taste and smell, further enhancing glycoprotein secretion in the saliva, which in turn increases lubrication of the oral cavity.[2,3] Numerous drugs[4-6] act directly on the sympathetic and parasympathetic pathways, hence decreasing salivary output and modifying saliva quality without directly affecting the structure of the salivary glands, with resultant effects in the oral cavity.[7-9] Moreover, an additive effect has previously been observed[4] when several drugs are taken concomitantly by the same patient, as is often observed in the geriatric population. Unfortunately, drug-induced xerostomia is often neglected by physicians because it has long-term rather than immediate severe dental consequences.[10-14]

Xerostomia is defined as the subjective sensation of dryness of the mouth that usually implies a marked decrease in saliva secretion.[1] Mouth dryness is not a normal consequence of old age but may occur in as many as 90% of older patients due to the growing use of medications, including psychotropic drugs and β-adrenoceptor antagonists, and/or during the course of several pathological conditions, for example, dehydration, hypothyroidism, Parkinson's disease, early- and end-stage dementia, chronic obstruction of nasal breathing, Sjögren's syndrome and/or diabetes mellitus.[1,10-12,15-17] As a result, retention of dental prostheses is decreased,[18] and mucosal dehydration and reduced lubrication in the oral mucosa may occur.[19] Other complications include bad breath and mouth ulcers;[11] extensive dental caries; mucosal atrophy and burning sensation; compromised speech, chewing and swallowing; and reduced or altered taste sensation, with resultant restrictions in daily activities and social life.[11,12,17-21] While <6% of older patients spontaneously complain of dry mouth[11,12,16,17] and xerostomia has theoretically not been considered part of aging, up to 50% of glandular tissue undergoes involution in older patients in conjunction with decreased concentrations of sodium, mucin and immunoglobulin in saliva.[22,23] Hence, studies of the management of xerostomia should specifically address older individuals.

Management of xerostomia includes symptomatic relief, prevention or correction of the sequelae of saliva hypofunction and treatment of any underlying disease.[15,16,20] Adequate hydration of oral tissues (frequent sips of water) is the standard treatment for xerostomia. The different modalities available in the management of xerostomia include products destined to stimulate the production of saliva (e.g. sialogogues such as pilocarpine and cevimeline [potent muscarinic receptor agonists that enhance saliva secretion], masticatory stimulants, and administration of gustatory substances), artificial saliva and saliva substitutes.[15] However, use of oral pilocarpine may not be suitable in the geriatric population because of numerous associated parasympathomimetic adverse effects observed, for example, hyperhidrosis, urgent micturition, rhinitis, tachycardia and even hypertension.[24] Saliva substitutes, which are typically based on aqueous electrolyte solutions, can contain animal mucins or carboxymethylcellulose, are associated with variable results and have poor acceptability to some patients.[25] In addition, prolonged administration of citric or malic acid contained in some of these formulations may lead to dental demineralisation and dental loss, especially in the older patient with often poor denture hygiene.[13]

Oxygenated glycerol triester (OGT) oral spray (Aequasyal®, Eisai SAS, Paris, France)[1] is a new oral lubricant for the treatment of dry mouth that is neither a saliva substitute nor a saliva stimulant. OGT spray has the property of adherence to the oral mucosa, forming a lipid film that protects against mechanical trauma, and may help to reduce moisture loss from oral tissue. OGT contains no pharmacological ingredients and consists only of the lubricant compound OGT (94.4%), silicon dioxide (1.5%) and alimentary grade flavouring agents

1 The use of trade names is for product identification purposes only and does not imply endorsement.

(4.1%). In the current study, we hypothesised that OGT oral spray might be effective in the relief of the subjective symptoms and objective signs of dry mouth in older people hospitalised in long-term care facilities.

Patients and Methods

Materials

OGT oral spray was kindly provided by the sponsor (Laboratoires Carilène, Montesson, France). The positive control Saliveze® was an aqueous electrolyte-containing solution (calcium chloride 0.15 mg/mL, magnesium chloride 0.05 mg/mL, sodium chloride 0.05 mg/mL, potassium chloride 1.2 mg/mL, sodium phosphate 0.28 mg/mL and sorbitol 30 mg/mL in purified water) purchased from Wyvern Medical Limited (Herefordshire, UK). Each bottle of OGT oral spray contained 20mL and each bottle of Saliveze® contained 50mL of solution.

Subjects, Aim and Study Design

Our objective was to evaluate the clinical efficacy and acceptability of OGT oral spray in the relief of signs and symptoms of xerostomia compared with Saliveze®. The latter was chosen as the reference product because it is a standard, commercially available treatment for dry mouth and is supplied as an oral spray similar to OGT spray. A 2-week, randomised, open-label, parallel-group design was employed. Forty-one patients with xerostomia aged ≥70 years and hospitalised in long-term care facilities were included in the study. Patients were enrolled after written informed content was obtained and then randomly assigned to either OGT or Saliveze® spray treatment for 2 weeks. Patients with oral candidiasis (as diagnosed by *Candida* counts obtained from an unstimulated whole saliva sample), dental infection, recent and/or ongoing head or neck radiotherapy, Sjögren's syndrome, a life-threatening pathological condition and those participating in another clinical trial at the time of the study were excluded from the trial.

Xerostomia was diagnosed by means of a patient-based questionnaire and measurement of saliva volume using a sialometer (test of saliva weight absorbed ≤0.5g/5 min) at baseline and after stimulation by chewing gum (showing a mean saliva flow rate of ≤0.2 mL/min and ≤0.5 mL/min, respectively).[20,21,26,27] Patients in the study also completed a questionnaire to assess symptoms of xerostomia at baseline. In addition, an oral soft tissue examination was conducted by a dental hygienist in a blinded fashion and included an objective evaluation of the lips, tongue, hard and soft palate, gingiva, mucobuccal fold areas, buccal mucosa and floor of the mouth using a four-point ordinal scale as follows: 0 = normal, 1 = mild, 2 = moderate, 3 = severe defect.[20,21]

Application of the oral lubricant and the saliva substitute was standardised. In brief, each patient was instructed to use one or two sprays of the assigned product at least five times per day, with nursing help as necessary to ensure that both treatments were applied correctly and consistently. The frequency of each product use was recorded. Spray bottles were weighed prior to dispensing to the patients and at the end of the treatment period to assess the quantity of the product used and treatment adherence. This study was approved by the Local Research Ethics Committee of Versailles, France and was registered on the ClinicalTrials.gov registry (NTC00350350).

Clinical Measurements and Questionnaires

The primary outcome variable was patient-based dry mouth scores as evaluated by a self-rated, 10cm long visual analogue scale (VAS) score recorded on day (D) 0 and D14. The latter was chosen as the primary endpoint because it was a specific, sensitive and reproducible criterion,[24-28] consistent with the main objective of the current clinical trial. Anchor points for the VAS score were 0 representing normal (i.e. no dry mouth symptoms) and 10 representing "the worst imaginable" dry mouth symptoms. Secondary outcome variables included patient-based perception of changes in other dry mouth symptoms (i.e. chewing, swallowing and speech difficulties as well as taste and burning sensations) using a self-rated, 10cm long VAS. In addition, oral tissue condition (redness and dryness of the tissues, degree of inflammation) was recorded on a four-point ordinal scale at D14 by the dental hygienist in a blinded fashion.[20,21]

Subjective assessment of xerostomia was performed at baseline and at D14 as dichotomous responses to a questionnaire and included several criteria such as diurnal and nocturnal mouth dryness, sleep disturbances due to mouth dryness, bad taste sensations, use of saliva substitutes, as well as questions about restrictions in social life, i.e. "Do you avoid speaking to people because of your dry mouth?" and "Do you stay in your room because of your dry mouth?". Other variables, such as the number of sprays required by patients per day and the time interval between each spray, were also recorded.

Evaluation of Treatment Tolerance and Acceptability

Taste was evaluated using a 10cm long VAS. Adverse events were recorded by the investigators.

Statistical Analysis

Based on previously published studies[26,28] and assuming a within-group standard deviation (SD) of 1cm in VAS score, a power of 85% and a type 1 error rate of 0.05, a sample size of 20 patients in each treatment arm was calculated as being necessary to demonstrate an effect size of 0.75.

Statistical analysis was conducted using the SPSS version 12.0 for Windows (SPSS Inc., Chicago, IL, USA). Results were expressed as mean ± SD or median ± SD, as appropriate, for continuous variables. Two-tailed comparisons were made between treatment groups with respect to demographics and efficacy parameters, according to the intent-to-treat principle, and between-treatment differences were presented as 95% confidence intervals. Analysis of covariance (ANCOVA), using the study group assignment as factor and baseline dry mouth VAS scores as covariate, was performed to reveal whether adjusted D14 dry mouth scores differed significantly between treatments. This was followed by Scheffe's test adjusted for multiple comparisons to determine the level of significance of differences (if any) between the two treatment groups in VAS scores relating to the effectiveness of the spray at D14 for the respective variable. Results were presented as percentages for nominal variables, and chi-squared (χ^2) or Fisher's Exact tests, as appropriate, were used to determine the significance of differences (if any) between dichotomous response variables. Between-treatment comparisons at D14 regarding mouth condition overall acceptability, oral spray taste and acceptability as evaluated by VAS score were performed using the non-parametric Mann-Whitney U test. For all comparisons, a p-value of ≤ 0.05 was considered statistically significant.

Results

Demographic and Baseline Characteristics

Between November 2003 and December 2004, 41 patients (22 in the OGT group, 19 in the Saliveze® group; 28 women and 13 men, sex ratio = 2.15) with xerostomia, as assessed by the questionnaire and measurement of saliva output, were enrolled and all but one completed the entire study. However, the only patient (OGT group) lacking data for D14 was included in the final analysis on the intent-to-treat principle and baseline values were assigned for the missing data. Mean (± SD) age (84 ± 7 years, range 70–94 years), weight (64 ± 12kg, range 43–90kg), height (161 ± 7cm, range 145–178cm) and saliva flow rate (0.03 ± 0.01 mL/min, range 0.01–0.05 mL/min) did not differ between treatment groups (p = 0.08, 0.96, 0.94 and 0.92, respectively, on the two-tailed, unpaired Student's t-test). Likewise, the sex ratio did not differ between treatment groups (p = 0.99, χ^2 test). Medical history taking revealed cardiovascular disease in 68% of patients, hypertension in 41%, psychiatric disorders in 34%, irritable bowel syndrome in 34%, arthritis in 34%, cancer in 12% and chronic obstructive pulmonary disease in 10% of patients. Eighty-one drugs, accounting for a total of 173 prescriptions (i.e. 4.22 drugs per patient), were taken by patients at the time of the study and the rate of such medication use did not differ between groups. Among these, 148 drugs usually associated with dry mouth symptoms[4] were prescribed; these included diuretics, antihypertensive and anti-arrhythmic drugs (furosemide, n = 40, hydrochlorothiazide, n = 15, rilmenidine, n = 10, metoprolol, n = 5, amiloride, n = 1), psychotropic drugs (alimenazine, n = 12, zopiclone, n = 10, acepromazine, n = 8,

Table I. Baseline and day (D) 14 degree of xerostomia as determined by patients using a self-rated, 10cm long visual analogue scale (VAS)[a]

Item	Baseline (cm)		D14 (cm)		Treatment difference at D14
	OGT (n = 22)	Saliveze® (n = 19)	OGT (n = 22)	Saliveze® (n = 19)	[cm] (95% CI)
Mouth dryness	7.4 ± 1.5	6.6 ± 1.5	2.5 ± 1.5	4.6 ± 1.3	2.1 ± 0.1 (1.9, 2.3)*
Chewing difficulties	4.9 ± 3.7	4.0 ± 3.9	1.3 ± 1.2	1.9 ± 1.8	0.7 ± 0.2 (−0.4, 0.9)
Swallowing difficulties	6.5 ± 2.5	6.1 ± 2.3	1.8 ± 1.5	3.6 ± 1.8	1.8 ± 0.3 (1.5, 2.1)*
Speech difficulties	5.1 ± 3.4	4.3 ± 3.4	1.8 ± 1.4	2.9 ± 1.6	1.1 ± 0.2 (1.0, 2.4)**
Taste alteration	5.1 ± 3.5	4.0 ± 3.5	1.8 ± 1.4	1.8 ± 1.5	0.1 ± 0.1 (−0.2, 0.2)
Burning sensation	4.2 ± 3.3	3.2 ± 2.8	2.0 ± 1.5	2.6 ± 2.1	0.6 ± 0.5 (−0.3, 0.9)

a Data are presented as mean ± SD.

OGT = oxygenated glycerol trimester; * p = 0.001, ** p = 0.04, at D14 (analysis of covariance using baseline VAS scores as covariate).

clomipramine, n = 5, mianserin, n = 3, chlorpromazine, n = 2, tianeptine, n = 1) and proton pump inhibitors (omeprazole, n = 22, lanzoprazole, n = 8, pantoprazole, n = 6). Other medications taken included laxatives (n = 15) and cholesterol-lowering drugs (n = 10).

Most patients complained of moderate to severe dry mouth at baseline, as measured on the 10cm long VAS (table I). No difference was noted between the two treatment groups ($p > 0.16$, ANCOVA). Analysis of the dichotomous responses recorded in the subject questionnaire revealed no statistically significant difference between the two treatment groups at baseline. Overall, 98% (40/41) of patients complained of diurnal mouth dryness and 76% (31/41) complained of nocturnal mouth dryness, which was associated with sleep disturbances and early wake-up in 48% (20/41) of patients ($p = 0.45$ between groups, Fisher's Exact test). Thirty-one percent (7/22) of patients in the OGT group and 16% (3/19) of patients in the Saliveze® group complained of bad taste in the mouth ($p = 0.29$ between groups, Fisher's Exact test). Consequently, 10% of patients declared that they usually avoid speaking to people but only 2.4% of them declared staying in their room because of dry mouth. Eighty-three percent of patients (34/41) were wearing a denture (18 in the OGT group vs 16 in the control group). Denture retention was affected by mouth dryness in 53% (21/41) of patients ($p = 0.31$ between treatment groups at baseline, Fisher's Exact test).

The objective assessment of patients' oral condition recorded by the dental hygienist in a blinded fashion using a four-point ordinal scale is presented in table II. At baseline, 100% of patients presented with dry mouth, considered by the dental hygienist to be moderate or severe in 85% of cases. Mild or moderate oral mucositis was documented in 39% (16/41) of patients. Overall, the oral mucosa was red and/or sticky and presented with at least one lesion in 49% of patients at baseline (20/41). Up to 59% of patients (24/41) had damaged lips and/or a thickened tongue and 76% of patients (31/41) had viscous and/or foamy saliva leading to moderate difficulties with speech related to dry mouth. No differences were noted between treatment groups at baseline ($p > 0.4$ for all comparisons, Fisher's Exact test).

Efficacy of Oxygenated Glycerol Triester Spray Based on the Primary and Secondary Endpoints at Day (D) 14

Of the six symptoms assessed by the VAS, OGT was significantly superior to Saliveze® in three items, i.e. mouth dryness (the primary endpoint), swallowing difficulties and speech difficulties, after adjustment for differences that existed at baseline using the ANCOVA model (table I). Likewise, the mean VAS score for overall sensation of symptom relief at D14 was significantly lower in the OGT spray group compared with Saliveze® (4.6 ± 2.9 vs 7.3 ± 3.9, respectively; mean difference, 2.7 ± 1.2, 95% CI 1.9, 3.8; $p = 0.001$). The sensation of improvement started on the first day of treatment in 23% versus 18% of patients and on the second day of treatment in 53% and 27% of patients treated with OGT and Saliveze®, respectively ($p = 0.49$ between groups, χ^2 test), and did not differ between day and night in 73% of patients ($p = 1.00$, Fisher's Exact

Table II. Baseline and day (D) 14 objective assessment of the oral tissue condition as recorded by a dental hygienist in a blinded fashion using a four-point ordinal scale[a]

Item	Baseline (cm)		D14 (cm)		95% CI for the difference at D14	p-Value[b]
	OGT (n = 22)	Saliveze® (n = 19)	OGT (n = 22)	Saliveze® (n = 19)		
Overall dryness of mouth	2.1 ± 0.7	2.0 ± 0.6	0.9 ± 0.6	1.5 ± 0.6	0.4, 0.8	0.001
Dryness of oral mucosa	2.0 ± 0.7	1.8 ± 0.5	0.8 ± 0.6	1.3 ± 0.6	0.3, 0.9	0.01
Inflammation of oral mucosa	1.7 ± 0.9	1.2 ± 0.8	0.8 ± 0.5	0.8 ± 0.8	−0.2, 0.3	0.63
Redness of oral mucosa	1.5 ± 0.8	1.5 ± 1.1	0.6 ± 0.5	0.6 ± 0.6	−0.03, 0.1	0.66
Stickiness of oral mucosa	1.5 ± 0.7	1.5 ± 0.8	0.4 ± 0.5	0.8 ± 0.5	0.2, 0.5	0.005
Dullness of oral mucosa	1.3 ± 0.4	1.7 ± 0.7	0.3 ± 0.5	1.0 ± 0.5	0.6, 0.8	0.001
Severity of mucositis	0.5 ± 0.7	0.6 ± 0.9	0.0 ± 0.0	0.3 ± 0.4	0.1, 0.5	0.01
Oral mucosal abrasion	0.8 ± 0.8	0.6 ± 0.8	0.2 ± 0.4	0.3 ± 0.4	−0.1, 0.1	0.53
Damaged lips	0.8 ± 0.8	0.9 ± 1.0	0.3 ± 0.5	0.5 ± 0.6	−0.2, 0.25	0.11
Thickened tongue	0.8 ± 0.8	0.7 ± 0.7	0.1 ± 0.3	0.4 ± 0.5	0.2, 0.4	0.03
Deficiency of saliva	1.9 ± 0.7	2.0 ± 0.7	0.9 ± 0.5	1.1 ± 0.6	−0.2, 0.3	0.14
Viscosity of saliva	0.9 ± 0.8	1.3 ± 0.8	0.3 ± 0.5	0.7 ± 0.6	0.3, 0.6	0.01
Foamy saliva	0.4 ± 0.7	0.5 ± 0.7	0.1 ± 0.3	0.2 ± 0.4	−0.1, 0.2	0.28
Halitosis (bad breath)	0.4 ± 0.6	0.4 ± 0.6	0.1 ± 0.3	0.2 ± 0.4	−0.1, 0.2	0.28
Speech difficulties	0.6 ± 0.7	0.7 ± 0.9	0.2 ± 0.4	0.5 ± 0.5	0.2, 0.4	0.04
Saliva and crusting at corners of mouth	0.4 ± 0.5	0.5 ± 0.7	0.0 ± 0.0	0.2 ± 0.4	−0.1, 0.3	0.06

a Data are presented as median ± SD of the score obtained by either treatment group at baseline and D14, respectively.

b p-Value for the respective item (analysis of covariance using baseline score as covariate).

OGT = oxygenated glycerol triester.

test). However, OGT spray prevented patients from night awakening in 33% of patients compared with only 5% of patients treated with Saliveze® ($p = 0.03$, Fisher's Exact test). After a single administration, both oral sprays were effective for 2–4 hours in 85% of patients in each group ($p = 0.88$, χ^2 test) and no additional oral spray was administered on any day by 60% of patients ($p = 0.67$ between treatment arms, Fisher's Exact test).

Patient-Based Assessment of Symptoms at D14 Using Responses to a Dichotomous Questionnaire

Eighty-one percent of patients treated with OGT declared that their mouth dryness had been substantially improved compared with 68% of patients treated with Saliveze® ($p = 0.76$, Fisher's Exact test). Likewise, OGT spray improved chewing, swallowing and speech in 48%, 71% and 38% of cases, respectively, versus 16%, 15% and 26% of patients treated with Saliveze® ($p = 0.15$, 0.002 and 0.67, respectively, Fisher's Exact test). Taste, burning sensation and items related to social life restriction, including dichotomous responses to questions such as "Do you stay in your bedroom more because of your dry mouth?" and "Do you avoid speaking to people because of your dry mouth?" were overall improved by both oral sprays in up to 71% of patients according to a patient-based assessment of symptoms ($p > 0.33$ for all comparisons, Fisher's Exact test). At D14, 68% of patients treated with Saliveze® still preferred to stay in their room because of mouth dryness, as compared with 38% of patients treated with OGT, but this difference did not reach statistical significance ($p = 0.06$, Fisher's Exact test). Among patients wearing a denture, OGT spray improved denture retention in 44% of patients treated with OGT versus 36% of those treated with Saliveze® ($p = 0.38$, Fisher's Exact test). Overall, 81% of patients felt better often using OGT as compared with only 58% of those treated with Saliveze® ($p = 0.03$, Fisher's Exact test). Likewise, 76% of patients treated with OGT experienced quality-of-life improvement compared with 21% of patients receiving Saliveze® ($p = 0.002$, Fisher's Exact test).

Objective Assessment of Oral Tissue at D14

Table II presents data relating to the objective assessment of the patients' oral tissue condition as recorded by the dental hygienist in a blinded fashion at D14 using a four-point ordinal scale. Among the 16 items objectively measured and shown in table II, local improvement in dryness (95% CI 0.4, 0.8; p = 0.001), stickiness of the oral mucosa (95% CI 0.2, 0.5; p = 0.005), dullness of the oral mucosa (95% CI 0.6, 0.8; p = 0.001), severity of mucositis (95% CI 0.1, 0.5; p = 0.01), thickened tongue (95% CI 0.2, 0.4; p = 0.03) and viscosity of saliva (95% CI 0.3, 0.6; p = 0.01) were significantly more improved with OGT than with Saliveze® at D14. Consequently, speech difficulties were also significantly improved with OGT (95% CI 0.2, 0.4; p = 0.04) [table II].

Treatment Tolerance and Acceptability

No serious adverse events that could be related to either study product were reported. Minor adverse events were reported in four patients (9.8%) and included nausea (one patient in the Saliveze® group) and unpleasant taste (two patients in the Saliveze® group and one in the OGT group).

Both oral sprays were rated easy to use by 83% of patients. At the end of the study, 76% of patients using OGT said they were willing to continue using OGT after the study versus 47% of patients treated with Saliveze® (p = 0.06, χ^2 test). The taste of OGT was preferred by patients over that of Saliveze®, according to the mean VAS results (7.2 ± 2.2 vs 5.8 ± 2.9, respectively; mean difference, 1.4 ± 0.6, 95% CI 1.2, 1.9; p = 0.04).

Discussion

In clinical practice, xerostomia is often neglected by both clinicians and patients, presumably because the efficacy of currently available therapeutic options is highly unpredictable.[14] In the current study, extensive evaluation of clinically relevant, accessible and reproducible subjective and objective symptoms of xerostomia[4,12,14,16,20] in older institutionalised patients with severe hyposalivation leading to sticky oral mucosa, mucositis, damaged lips and impaired quality of life as a result of taste alteration, speech difficulties, bad breath and social life restrictions demonstrated that OGT oral spray was significantly superior to Saliveze® in improving mouth dryness, swallowing and speech. Furthermore, OGT also resulted in significantly greater improvements in oral tissue condition and saliva viscosity as assessed by a blinded dental hygienist after 14 days of treatment. Both oral sprays were also well tolerated although OGT was perceived to have a better taste than Saliveze®.

There is considerable difficulty in making the initial clinical decisions as to whether a given patient has salivary gland hypofunction and hence requires additional salivary gland evaluation and may be eligible for treatment. In this regard, we used previously validated measures (e.g. dryness of lips and buccal mucosa), previously validated tools (e.g. a 10cm long VAS and a four-point ordinal scale) and a validated cut-off of salivary flow-rate to identify and enrol patients with dry mouth into the current clinical trial.[29] Thus, the enrolled population had clinical relevance because patients were included primarily on the basis of saliva production, as measured by a sialometer to confirm hyposalivation at D0 (but not at D14 as OGT is not a saliva stimulant). Nevertheless, the current study has several limitations, partly related to the difficulties inherent in designing a clinical trial in older institutionalised patients and evaluating treatments in a condition as subjective as xerostomia. Consideration of the short-term parallel-group design of the current trial points to the need for a further longer clinical study to demonstrate the long-term benefit of OGT oral spray in older patients. Furthermore, a randomised, double-blind, controlled trial conducted in a larger cohort of older patients would have been more methodologically sound; however, this is unrealistic in the current setting because of the different textures of the two products (Saliveze® is an aqueous solution while OGT is a viscous oral lubricant). Finally, the purpose of the current study was to compare the efficacy of OGT oral spray in the relief of symptoms of xerostomia with that of a currently marketed saliva substitute, rather than to the reference drug pilocarpine.[15] This reflects the fact that OGT is not a saliva stimulant and treatment efficacy cannot be correlated with increase in saliva output, to the best of our knowledge.[1,15,16,20,26,28]

Although more than 500 medications have been reported to cause dry mouth as an adverse effect, only a small number have been demonstrated to result in actual reduced salivation; these include tricyclic antidepressants, histamine H_1 receptor antagonists (antihistamines), antihypertensives and diuretics.[4] Most of these drugs are often concomitantly prescribed in older patients,[5,6,16] as observed in the current study. Moreover, an additive dry mouth adverse effect has previously been observed[4] when several such drugs are co-administered in the same patient, a situation that is often observed in the geriatric population and was documented in the current study. Increasing use of medication in this particular patient population is clearly exacerbating mouth dryness and patients' oral condition, although this was not evaluated in our study of daily life in institutionalised patients taking numerous concomitant medications.

As shown in the current study, in which several validated assessment scales were utilised in addition to measurement of saliva output, evaluation of dry mouth symptoms should be carried out in a systematic fashion, especially in older adults.[9,12,16,20] The goals are to relieve symptoms, prevent or correct the sequelae of salivary dysfunction and treat any underlying disease. Adequate hydration of the oral mucosa in order to moisten and cleanse the mucosal surface and hydrate the oral tissue is essential but not sufficient. European formulations (not available in the US) of saliva substitutes that contain animal mucins have been preferred to products with a carboxymethycellulose base alone in some but not all patients.[9,30] However, in some authors' experience,[9,30] most patients find that frequent sipping of fluids is superior and more aesthetically acceptable than use of saliva substitutes. The current study does not confirm these observations, as 83% of our patients rated both oral sprays as easy to use, product acceptability was high and 76% of patients were willing to continue using the oral sprays after the end of the study. In a previous study conducted in patients with advanced cancer who had undergone radiation therapy, the efficacy of an animal mucin-based saliva substitute was not significantly different from that of chewing gum, a salivary stimulant, in the management of xerostomia.[26] However, this study was underpowered, lacked many data in the final analysis, and enrolled patients with moderate mouth dryness (mean VAS score obtained in each group at baseline was 3.25cm). In addition, the mucin contained in the study product was derived from porcine gastric mucosa, and therefore may not be suitable for Jews, Muslims and various other groups.[28]

Conclusion

Dry mouth is a common complaint and a significant problem in geriatric clinical practice that deserves to be as aggressively evaluated as it is in younger people. Given the numerous mechanisms involved in xerostomia in older patients, use of an oral lubricant might be suitable for the treatment of dry mouth. In this regard, OGT oral spray was superior to a currently marketed aqueous saliva substitute containing electrolytes (Saliveze®) in improving mouth dryness, oral tissue condition and social life in a long-term hospitalised geriatric population. This treatment may therefore be proposed in older institutionalised patients with symptoms of dry mouth, even in those treated with multiple concomitant medications known to induce xerostomia. With the number of older patients expected to increase worldwide,[31] further studies will be welcomed to confirm that the benefit of OGT may be prolonged over time in the treatment of xerostomia. Maintenance of adequate oral hygiene and hydration to prevent clinical complications such as increased dental caries, monilial infection, dysgeusia and tooth sensitivity, all of which are often observed in older patients with xerostomia, is an important goal.

Acknowledgements

This study was funded by Laboratoires Carilène, Montesson, France. The authors are indebted to the nurses at the Department of Geriatry, Clinique Leopold Bellan, Magnanville, France for their precious contribution to the study. Dr Stéphane Mouly received an honorarium from Laboratoires Carilène for preparation of the article. Dr Anne-Claude Coudert and Dr Stéphane Desjonquères are employees of Laboratoires Carilène. The other authors have no conflicts of interest that are directly relevant to the content of this study.

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